# Chapter 11: Rubella

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## I. Disease description

Rubella is a viral illness caused by a togavirus of the genus *Rubivirus*. The rubella rash, a diffuse maculopapular rash consisting of small, fine pink spots, is sometimes misdiagnosed as measles or scarlet fever and occurs in up to 50% of rubella-infected persons. Children usually develop few or no constitutional symptoms, but adults may experience a 1–5 day prodrome of low-grade fever, headache, malaise, mild coryza, and conjunctivitis. Postauricular occipital and posterior cervical lymphadenopathy is characteristic and precedes the rash by 5–10 days. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. Rare complications include thrombocytopenic purpura and encephalitis.

When infection occurs during pregnancy, especially during the first trimester, the risk of fetal infection may be as high as 90%, often resulting in congenital rubella syndrome (CRS). Consequences of CRS include abortions, miscarriages, stillbirths, and severe birth defects. Up to 20% of the infants born to mothers infected during the first half of pregnancy have CRS. The most common congenital defects are cataracts, heart disease, sensorineural deafness, and developmental delay. See Chapter 12, "Congenital Rubella Syndrome," for more details.

## II. Background

The number of reported cases of rubella in the United States has declined more than 99% from 57,686 cases in 1969 to a provisional total of 345 cases in 1998. The proportion of cases among adults aged $\geq$20 years has risen from 29% of cases in 1991 to 74% of cases in both 1997 and 1998. In 1998, 267 (83%) of 323 reported rubella cases of known race/ethnicity were among persons of Hispanic ethnicity.[1] Despite routine rubella vaccination among children, rubella outbreaks continue to occur among members of religious communities that traditionally refuse vaccination[2,3] and among adults from countries without a history of routine rubella vaccination programs.

## III. Importance of rapid case identification

Prompt identification of suspected or confirmed cases of rubella is important to avoid exposure of susceptible pregnant women.

## IV. Importance of surveillance

Surveillance data are used to identify groups of persons or areas in which additional disease control efforts (such as immunization) are required to reduce disease incidence, and to evaluate the effectiveness of disease prevention programs and policies.

## V. Disease reduction goals

As part of the proposed Healthy People 2010 objectives, a goal was established for the elimination of indigenous rubella and CRS in the United States by the year 2010.[4]

## VI. Case definitions

The following case definition for rubella has been approved by the Council of State and Territorial Epidemiologists (CSTE), and was published in May 1997 (Appendix 1).[5]

### Clinical case definition

An illness that has all of the following characteristics:

- Acute onset of generalized maculopapular rash
- Temperature >99°F(37.2°C), if measured
- Arthralgia/arthritis, lymphadenopathy, or conjunctivitis

### Laboratory criteria for diagnosis

- Isolation of rubella virus, or
- Significant rise between acute and convalescent-phase titers in serum rubella immunoglobulin G antibody level by any standard serologic assay, or
- Positive serologic test for rubella immunoglobulin M (IgM) antibody.

### Case classification

**Suspected:** Any generalized rash illness of acute onset.

**Probable:** A case that meets the clinical case definition, has no or noncontributory serologic or virologic testing, and is not epidemiologically linked to a laboratory-confirmed case.

**Confirmed:** A case that is laboratory confirmed or that meets the clinical case definition and is epidemiologically linked to a laboratory-confirmed case.

**Comment.** Serum rubella IgM test results that are false positive have been reported in persons with other viral infections (e.g., acute infection with Epstein-Barr virus [infectious mononucleosis], recent cytomegalovirus infection, and parvovirus infection) or in the presence of rheumatoid factor.[6,7] Patients who have laboratory evidence of recent measles infection are excluded.

**Asymptomatic confirmed.** A case in a person who is asymptomatic that is laboratory confirmed and is epidemiologically linked to a laboratory-confirmed

case that is clinically consistent with rubella.

**Importation Status.**

**Indigenous case**. Any case which cannot be proved to be imported.

**Imported case.** A case which has its source outside the state.

- Importation from another country — onset of rash is within 14–23 days of entering the United States.
- Importation from another state — this requires documentation that the person had face-to-face contact with a case of rubella outside the state, or was out of the state for the entire period when he or she might have become infected (14–23 days before rash onset).

## VII. Laboratory testing

Diagnostic tests used to confirm acute or recent rubella infection or CRS include serologic tests and virus cultures.

***The only reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, a significant rise in IgG antibody from paired acute and convalescent sera, or a positive viral culture for rubella.***

Acute rubella infection can be confirmed by a significant rise in IgG antibody titer in acute and convalescent serum specimens, by the presence of serum rubella IgM, or by a positive rubella virus culture. Sera should be collected as early as possible (within 7–10 days) after onset of illness, and again at least 7–14 days (preferably 2–3 weeks) later. IgM antibodies may not be detectable before day 5 after rash onset. In case of a negative rubella IgM and IgG in specimens taken before day 5 repeat serologic testing. Virus may be isolated from the pharynx from 1 week before to 2 weeks after rash onset.

False-positive serum rubella IgM tests have occurred in persons with parvovirus infections or positive heterophile test (indicating infectious mononucleosis), or with a positive rheumatoid factor (indicating rheumatologic disease).[6,7] When a false-positive rubella IgM is considered, a rheumatoid factor, parvovirus IgM, and heterophile test should be done to rule out a false-positive rubella IgM test result.

Because many rash illnesses may mimic rubella infection and because up to 50% of rubella infections may be subclinical, the only reliable evidence of acute rubella infection is the presence of rubella-specific IgM antibody, demonstration of a significant rise in IgG antibody from paired acute and convalescent sera, or a positive viral culture for rubella.

For additional information on laboratory testing for the surveillance of vaccine-preventable diseases, see Chapter 19.

### Serologic testing

The serologic tests available for laboratory confirmation of rubella infections vary among laboratories. The following tests are widely available and may be used for screening for rubella immunity and/or laboratory confirmation of disease. The

state health department can provide guidance on available laboratory services and preferred tests.

- **Enzyme immunoassay (EIA)**. EIA is sensitive, widely available, and relatively easy to perform. It can also be modified to measure IgM antibodies. Most of the diagnostic testing done for rubella antibodies uses some variation of the EIA.

- **Hemagglutination inhibition (Hi) test**. This once was the "standard" and most commonly used technique. It is sensitive and simple to perform, and allows for either screening or diagnosis (if paired acute and convalescent sera are tested). A four-fold rise or greater in HI antibody titer in paired sera is diagnostic of recent infection. The test may be modified to detect rubella-specific IgM antibody indicative of primary infection.

- **Passive hemagglutination antibody (PHA) test** (e.g., Rubacell). The PHA is not quite as sensitive as the HI test and misses low titers (<1:16 which represent approximately 5%–10% of the normal adult population with positive HI tests). It is, however, easily and rapidly performed and is a useful screening test, but is not recommended as a diagnostic test.

- **Latex agglutination (LA) test**. The 15-minute LA test appears to be sensitive and specific for screening.

- **Immunofluorescent antibody assays (IFA)**. IFA is a rapid and sensitive assay. Commercial assays for both IgG and IgM are available in the United States. Care must be taken with the IgM assay to avoid false-positive results due to complexes with rheumatoid antibody.

- **Complement fixation (CF)**. Since CF antibodies are detectable after HI antibodies have already been made, a four-fold rise in CF antibodies between acute and convalescent sera may be demonstrated when HI titers have already stabilized, indicating an acute primary infection. CF should not be used for screening.

**Virus cultures**

Rubella virus can be isolated from nasal, blood, throat, urine, and cerebrospinal fluid specimens from rubella and CRS cases (Appendix 17). Efforts should be made to obtain clinical specimens (pharyngeal swabs and urine) for virus isolation from all cases (or from at least some cases in each outbreak) at the time of the initial investigation. These specimens for isolation of rubella virus should be obtained within 4 days after rash onset.

**Molecular Typing**

Although virus isolation is rarely used as laboratory confirmation of rubella cases, rubella virus isolates are very important for surveillance. Molecular epidemiologic surveillance provides important information on 1) the origin of the

virus, 2) virus strains circulating in the U.S., and 3) whether these strains have become endemic in the U.S. In obtaining specimens for rubella molecular typing, collect pharyngeal swabs within 4 days of rash onset. Specimens for molecular typing from CRS cases should be collected as soon as possible after diagnosis. Appropriate specimens from CRS cases for molecular typing include pharyngeal swabs, cerebral spinal fluid, and cataracts from surgery. Strains for virus isolation should be sent to CDC for molecular typing as directed by the state health department.

## VIII. Reporting

Each state and territory has regulations and/or laws governing the reporting of diseases and conditions of public health importance (Appendix 2).[8] These regulations/laws list the diseases which are to be reported, and describe those persons or groups responsible for reporting such as health-care providers, hospitals, laboratories, schools, day care facilities, and other institutions. Contact your state health department for reporting requirements in your state.

### Reporting to CDC

Provisional reports of rubella and CRS cases should be sent by the state health department to CDC via the National Electronic Telecommunications System for Surveillance (NETSS) within 14 days of the initial report to the state or local health department. Reporting should not be delayed because of incomplete information.

### Information to collect

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may also be collected at the direction of the state health department.

- Demographic information, including country if origin and time of residence in the U.S.

- Vaccination status of cases including
  - —Number of doses of rubella vaccine
  - —Dates of vaccination
  - —If not vaccinated, reason for non-vaccination

- Risk factors for disease including
  - —Transmission setting (i.e., infection acquired in day care, school, workplace)
  - —Relationship to outbreak (i.e., is case part of an outbreak or is it a sporadic case)

- Source of exposure and travel history (i.e., import status [indigenous, international import or out-of-state import, state name, country name])

• Contact with a probable or confirmed case

• For women
  —If pregnant, pregnancy status
    -Number of weeks gestation at onset of illness
    -Prior evidence and/or date of serological immunity
    -Prior diagnosis and date of rubella
    -Date and specific titer result of prior serum rubella IgG titer
    -Pregnancy outcome, when available

• Clinical details including
  —Date of onset and duration of rash
  —Presence of fever, arthralgia/arthritis, lymphadenopathy, conjunctivitis
  —Date of onset of symptoms
  —Complications (e.g., encephalitis, arthritis/arthralgia, thrombocytopenia, death)

• Laboratory information including
  —Date and source of specimen sent for viral culture (e.g., pharynx, urine, blood)
  —Viral culture results (positive or negative for rubella virus)
  —Serologic test results for serum rubella IgM or IgG, with specific titer result, e.g., 1:256. (A positive serum rubella IgM or a four-fold or greater rise in acute and convalescent titers signifies an acute infection.)

***Clinical diagnosis of rubella is unreliable and should NOT be considered in assessing immune status.***

## IX. Vaccination

Live attenuated rubella virus vaccine is recommended for persons ≥12 months of age unless there is a medical contraindication such as severe immunodeficiency or pregnancy, there is documented evidence of rubella immunity as defined by serological evidence, (e.g., a positive serum rubella IgG), or there is documentation of immunization with at least one dose of rubella vaccine on or after the first birthday. **Clinical diagnosis of rubella is unreliable and should NOT be considered in assessing immune status.**

With use of combined measles-mumps-rubella vaccine (MMR) for measles vaccination under the currently recommended two-dose schedule, most children and adolescents now receive two doses of rubella vaccine. Rubella vaccine, as MMR, is recommended at 12–15 months of age. A second dose of MMR is recommended at 4–6 years of age.[9]

## X. Enhancing surveillance

The following activities may be undertaken to improve the detection and reporting of cases, and to improve the comprehensiveness and quality of surveillance for rubella. Additional guidelines for enhancing surveillance are given in Chapter 16.

**Promoting awareness that rubella and CRS still occur in the United States.** Efforts should be made to promote physicians' awareness of the possibility of rubella and CRS, especially when evaluating patients with suspected measles who have negative serologic tests for acute measles infection (i.e., negative serum measles IgM).

**Promoting awareness of high risks groups for rubella infection and CRS births.** Health-care providers should have a heightened index of suspicion of rubella and CRS births in individuals from countries without a history of routine rubella vaccination programs.

**Expanding laboratory testing.** Serologic testing for measles and rubella may be done simultaneously. All suspected cases of measles that have a negative serum measles IgM test should be tested for rubella IgM and IgG. All suspected cases of rubella should be tested for serum rubella IgM.

**Searching laboratory records.** Audits of laboratory records may provide reliable evidence of previously unreported serologically confirmed or culture-confirmed cases of rubella. This activity is particularly important during outbreaks in order to better define the scope of disease transmission in an area.

**Active surveillance.** In outbreak settings, active surveillance for rubella should be maintained for at least two incubation periods following rash onset of the last case. Following an outbreak of rubella, an active surveillance system for CRS should be established among health-care providers, clinics, and hospitals in the outbreak area beginning 6–9 months after the rubella outbreak.

**Monitoring surveillance indicators.** Regular monitoring of surveillance indicators including time intervals between diagnosis and reporting and completeness of reporting may identify specific areas of the surveillance and reporting system that need improvement.

1. The proportion of confirmed cases reported to the NNDSS with complete information.

2. The median interval between rash onset and notification of a public health authority, for confirmed cases.

3. The proportion of confirmed cases that are laboratory confirmed.

4. The proportion of confirmed cases among women of child-bearing age with known pregnancy status.

## XI. Case investigation

The goal of rubella case investigation is to prevent exposure of susceptible pregnant women to rubella, and thereby prevent cases of CRS. It is essential that potentially susceptible, exposed pregnant women be identified, evaluated,

and counseled. The Rubella Surveillance Worksheet (Appendix 18) may be used as a guideline in conducting a case investigation.

**Establish a diagnosis of rubella**. Because clinical diagnosis of rubella is unreliable, cases must be laboratory confirmed, especially if they are not epidemiologically linked to a laboratory-confirmed case.

The occurrence of a rubella-like illness in recently vaccinated persons can pose particular difficulties in the outbreak setting. Ten percent of recipients of rubella-containing vaccine may develop fever and rash approximately 1 week after vaccination, and vaccination of susceptible persons results in production of IgM antibody that cannot be distinguished from that resulting from natural infection. Recently vaccinated rubella IgM positive persons with a rubella-like illness should be classified as confirmed cases of rubella if they are epidemiologically linked to a laboratory-confirmed case. To distinguish between vaccine and wild virus rash, obtain nasopharyngeal or pharyngeal swabs within 4 days of rash.

**For adult women, obtain accurate pregnancy status.** All women of childbearing age who are contacts of a case should have their pregnancy status determined. If a pregnant woman is infected with rubella, immediate medical consultation is necessary. If a pregnant women is susceptible to rubella, precautions should be taken to prevent any exposure to persons infected with rubella; these activities may include ensuring rubella immunity of household contacts and isolation of women from settings where rubella virus has been identified.

**Obtain accurate and complete immunization histories.** Rubella case investigations should include complete immunization histories that document any doses of rubella-containing vaccine.

**Identify source of infection.** Efforts should be made to identify the source of infection for every confirmed case of rubella. Case-patients or their caregivers should be asked about contact with other known cases; in outbreak settings, such histories may often be obtained. Since many rubella cases (20%-50%) are asymptomatic, identification of a source will not always be possible. When no history of contact with a known case can be elicited, opportunities for exposure to unknown cases should be sought. Investigating sources of exposure should be directed to the place and time period in which transmission would have occurred. Such exposures may occur in colleges or universities, workplaces, and communities where unvaccinated persons congregate.

**Assess potential for transmission and identify contacts.** In recent outbreaks, transmission has occurred in households, communities, workplaces, and prisons. As part of the case investigation, the potential for further transmission should be assessed, and contacts (particularly susceptible pregnant women) of the case-patient during the infectious period (7 days before to 7 days after the onset of rash) should be identified.

**Obtain specimens for virus isolation.** Efforts should be made to obtain clinical specimens (nasopharyngeal swabs and urine) for virus isolation from all cases (or

from at least some cases in each outbreak) at the time of the initial investigation. These specimens for suspected rubella should be obtained within 4 days after rash onset. These isolates are essential for tracking the epidemiology of rubella in the United States, now that rubella virus may no longer continuously circulate in this country. By comparing isolates from new case-patients to other virus samples, the origin of particular virus types in this country can be tracked.[10] See Appendix 17 for procedure to follow in collection of specimens.

**Laboratory evaluation of exposed pregnant women.** When a pregnant woman is exposed to rubella, a blood specimen should be taken as soon as possible and tested for rubella IgG and IgM antibody. The specimen should be stored for possible retesting. A positive IgM response indicates recent or acute infection. A positive IgG result performed at the time of exposure most likely indicates immunity. If there is no IgG or IgM response, a second specimen should be taken 3 to 4 weeks later and tested concurrently for IgG with the first specimen. If the response is still negative, a third specimen should be obtained at 6 weeks, and again tested for IgG concurrently with the first. An IgG negative result at 6 weeks indicates that infection has not occurred. A negative response on the first specimen and a positive response on the second or third specimen indicates that infection has occurred. As long as the exposure to rubella continues, it is important to continue testing for IgG and IgM responses.

**Pregnancy Outcome Registry for women diagnosed with rubella during pregnancy.** All pregnant women infected with rubella during pregnancy should be followed to document the pregnancy outcome (e.g., termination, CRS, normal infant). Outcomes that are documented should be reported to the CDC.

## XII. Outbreak control

Aggressive response to rubella outbreaks may interrupt disease transmission and will increase vaccination coverage among persons who might otherwise not be protected. The main strategies are to define at-risk populations, to ensure that susceptible persons are rapidly vaccinated (or excluded from exposure if a contraindication to vaccination exists), and to maintain active surveillance to permit modification of control measures if the situation changes.

Control measures should be implemented as soon as at least one case of rubella is confirmed in a community. This approach is especially important in any outbreak setting where pregnant women may be exposed, such as prenatal and obstetric clinics. All persons at risk who cannot readily provide laboratory evidence of immunity or a documented history of vaccination on or after their first birthday should be considered susceptible and should be vaccinated if there are no contraindications.

In schools and other educational institutions, exclusion of persons without valid evidence of immunity may limit disease transmission and may help rapidly raise the vaccination level in the target population. All persons who have been exempted from rubella vaccination because of medical, religious, or other reasons also should be excluded from attendance. Exclusion should continue until 3 weeks after the onset of rash of the last reported case in the outbreak

setting.

Mandatory exclusion and vaccination of adults should be practiced in rubella outbreaks in medical settings because pregnant women may be exposed. ❖

## References


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